REMARKS

Claims 2-12, 17, 44-47 and 51-59 are pending in the application. Claims 2-9, 44, 45 and 51-59 have been amended. Support for the claim amendments may be found throughout the specification and claims as originally filed. No new matter has been added.

Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The cancellation of and/or amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicant reserves the option to further prosecute the same or similar claims in the present or another patent application.

Formal Matters

Applicants gratefully acknowledge the withdrawal of the election of species. In addition, Applicants wish to thank the Examiner for the withdrawal of the previous objections to claims 2, 44, 45 and 57-59, and for the withdrawal of the rejection of claims 10-11, 17, 46 and 47 under 35 U.S.C. § 112, second paragraph.

Claim Rejections under 35 U.S.C. §112 First Paragraph

Claims 2, 3, 4, 6, 10-12, 17, 44-47, 51-56 and 57-59 have been rejected on the ground that

> "...the specification, while being enabling for a method of identifying a compound which decreases p21 and cyclin D1 wherein the p21 fragment or derivative comprises SEQ ID NO: 2, 10, 28, 11 and 24, does not reasonably provide enablement for a method of identifying a compound which decreases binding between a derivative or analogue of p21 comprising SEQ ID NO: 4, 14 or xyLzF and a derivative of cyclin D1" (Office Action at p. 3)

Applicants traverse this rejection. With respect to SEQ ID NO: 4, claims 2 and 57, which are directed to a method of identifying a compound which modulates the interaction of p21 and cyclin D1, have been amended to remove reference to SEQ ID NO: 4. However, Applicants respectfully submit that independent claims 44 and 58, which are directed to a method of identifying a compound which modulates the interaction between *p21 and cdk4*, and independent claims 45 and 59, which are directed to a method of identifying a compound which modulates the interaction of *p21, cyclinD1 and ckd4* are fully enabled. The specification discloses that a p21 peptide fragment containing the amino acid sequence set forth in SEQ ID NO: 4 is capable of binding and forming a stable complex with cdk4 (see, for example, page 4, lines 10-11; page 6, lines 16-22; and page 53, lines 8-29).

With respect to SEQ ID NO: 14, Applicants respectfully submit that this sequence includes the amino acid residues involved in the binding of peptide 2 (SEQ ID NO:2) to cyclin

D1, and further defines those residues that may be substituted based on experimental evidence and knowledge of the crystal structure of the related protein, p27 (see page 7, line 25 to page 8, line 11). However, solely in the interest of expediting prosecution of the application, the claims have been amended to remove this sequence.

With respect to the sequence xyLzF, Applicants discovered that a stretch of five amino acids, RRLIF, contains the motif required for the interaction of p21, cdk4 and cyclinD1. Applicants further demonstrated that amino acid substitutions at certain positions within this motif retain the ability to bind both cdk4 and cyclin D1. For example, at pages 63-64 and in Figure 6, the specification presents data indicating that substitution of the first R retains partial binding activity, and that substitution at the second R or at I had no effect on binding. In order to expedite prosecution, the claims have now been amended to clarify that these substitutions may occur within the peptide KRRLIFSK (SEQ ID NO: 23), a peptide which was demonstrated to completely inhibit cyclin-Cdk4 activity.

Accordingly, in view of the remarks set forth above, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 2, 3, 4, 6, 10-12, 17, 44-47 and 51-59 were further rejected on the ground that the claimed subject matter is "overly broad in the recitation of 'derivative' and 'fragment' since insufficient guidance is provided as to which of the myriad of polypeptide species encompassed by the claim will retain the characteristics of p21 or cyclin D1" (Office Action, page 3).

Applicants respectfully traverse this rejection. To expedite prosecution, the claims have been amended to remove the term 'derivative.' However, the term "fragment" as used in the presently amended claims is fully enabled; the present specification provides the information necessary for one of skill in the art to determine the peptide fragments that can be used in the claimed methods. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §112, Second Paragraph

Claims 2, 3, 4, 6, 10-12, 17, 44-47 and 51-56 have been rejected as lacking sufficient written description on the ground that "[b]ecause of the use of the terms fragments, derivatives or analogues, the claims encompass proteins having one or more amino acid substitutions, deletions, insertions and/or additions made to cyclin D or p21." (Office Action, pp. 5-6)

Applicants traverse this rejection. However, to expedite prosectution, the claims have been amended to remove the terms "derivatives" and "analogues." Further, the claims have also been amended to specify that the first substance comprises a peptide fragment of 40 amino acids or less of p21, and specifically sets forth the structural characteristics of the p21 fragments that

are required to interact with cyclin D1 and/or Cdk4. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §103

All of the pending claims stand rejected as being unpatentable over WO 94/09135 (Beach *et al.*) in view of Xiong *et al.* (1993) for the reasons of record set forth in Paper No. 21, 10/22/2002. Applicants traverse this rejection as being improper essentially for the reasons of record which are hereby incorporated herein as if reiterated in full.

The presently claimed invention is directed to methods of identifying a compound that modulates the binding between p21 and cyclin D1 and/or Cdk4 using a p21 fragment of ***40 amino acids or less***. Beach *et al.* demonstrate that ***full-length*** p21 forms a complex with Cyclin D, PCNA and a CDK (*Cdk2, Cdk4 and Cdk5*), and speculate that one might prevent complex formation using general screening methods containing these components (p21, Cyclin D, PCNA and a CDK). Xiong *et al.* teach that full-length p21 is ***164 amino acids long*** (see page 701, column 2 and Figure 1). Neither of these references provide any details whatsoever regarding the specific interactions between these four components, and, in fact, Beach *et al.* state that "the experimental techniques in this study do not formally allow a distinction between the existence of multiple pair-wise interactions between each protein" (see page 14, lines 1-3). Nor do either of these references teach that lead one of ordinary skill to attempt to find compounds that modulate the interaction of p21 and cyclin D and/or cdk4 (as opposed to Cdk2 or Cdk5). Moreover, neither of these references even suggest using ***p21 fragments of 40 amino acids or less rather than full-length p21*** to identify compounds that modulate the interaction of p21 and cyclin D and/or Cdk4, let alone teach p21 fragments containing the sequences identified and claimed by Applicants.

In short, Beach *et al.* and Xiong *et al.* both disclose the use of ***full-length p21***. Neither of these references even suggest that one could or should modify the full-length p21 protein for any purpose, let alone for use in methods to identify compounds that modulate the interaction between p21 and cyclin D1 and/or Cdk4. Nor do they provide any basis from which one of ordinary skill would be able to predict with a reasonable expectation of success which fragments of p21 would be useful. It is well-established law that,

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art . . . Both the suggestion and the expection of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.,* 837 F.2d, 5 USPQ 1529 (Fed. Cir. 1988)

Thus, absent Applicants' disclosure, it would not have been obvious to one of ordinary skill to modify ***full-length p21*** to generate fragments of ***40 amino acids or less*** that could be used with any reasonable expectation of success in the presently claimed methods. Accordingly, Applicants respectfully submit that this rejection is improper and should be withdrawn.

SUMMARY

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. CCI-007USRCE from which the undersigned is authorized to draw.

Dated: March 24, 2004

Respectfully submitted,

By _____

Cynthia L. Kanik, Ph.D.
Registration No.: 37,320
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant